RESEARCH ARTICLE

Research Progress of Notch Signaling Pathway Related Diseases

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Abstract: Notch signal transduction pathway is one of the important pathways that affect the fate of cells. Adjacent cells transmit signals through Notch receptors to regulate the differentiation, proliferation and apoptosis of many kinds of cells, including stem cells. Affects organ formation and morphogenesis. Gene mutations of some molecules in Notch signaling pathway are related to the occurrence and development of many diseases. On the basis of in-depth study of Notch signal transduction pathway, using it as a target to design drugs for the treatment of related diseases, including cancer, CADASIL and other hereditary diseases, or the development of stem cell medical techniques. Surgical treatment of Alzheimer's disease (disease,AD), Parkinson's disease, diabetes mellitus and other cellular tissue dysfunction or impaired diseases has important scientific significance and application value.

Keywords: Notch; neoplasms; genetic diseases; stem cells

Notch gene was found in Drosophila in 1919 that a partial deletion of Notch gene caused a notch at the edge of the wing of Drosophila melanogaster, hence the name of Notch gene[1,2].Notch signal transduction pathways are widespread in vertebrates and non-vertebrates and are highly conserved in evolution. The binding of Notch receptor and ligand transmits Notch signal, which enlarges and solidifies the molecular differences between cells, and ultimately determines cell fate, affecting organogenesis and morphogenesis. Notch signal changes were also found to be closely related to the occurrence and development of many diseases, such as tumours, hereditary diseases, neurodegenerative diseases and cardiovascular diseases. Based on the in-depth study of the molecular mechanism of Notch signal and its related diseases, a drug design targeting the Notch signal pathway was carried out to treat Alzheimer's disease and to develop stem cell medical technology for the treatment of Alzheimer's disease. Parkinson's disease, diabetes mellitus and other cellular tissue dysfunction or damaged diseases have important scientific significance and application value. This paper deals with the Notch signal Progress in the study of conduction pathways and related diseases is reviewed.

1. Notch signal transduction pathway

1.1 Notch receptors and ligands

Notch receptor is a heterodimer composed of about 300 ku transmembrane,NTM subunits encoded by Notch gene. ECN and NTM bind together through non-covalent bonds. The interaction between ECN and NTM is Ca2 dependent[3]. The extracellular and intracellular domains of Notch receptors are highly conserved. The extracellular domain consists of 290.36 epidermal growth factor-like repeat sequences (epidermal growth factor-like re) in the anterior and posterior rows of Epidermal growth Factor (EGF). Peats, EGF-R) and three Lin/ Notch repeats (LNR)[4]. The existence of Notch ligand binding site[5] in the EGF-R domain plays an important role in maintaining the interaction between ECN and NTM[3]. The short extracellular structure of NTM subunit contains two conserved cysteine residues. Its intracellular domain includes RAM (RBP-J kappa associated molecular) domain), There are 7 cdc/ankyrin complex sequence, 2 nu-

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cleated signal region (NLS) and C terminal PEST junction domain (proline-glutamate- serine-threonine-rich domain)[4]. PEST is considered to be related to the stability of Notch receptor protein. Notch ligand is also expressed on the cell surface of single-transmembrane egg white, adjacent cells through the Notch receptor binding to the ligand transfer Notch signal. There are two Notch ligands, Delta and Serrate. in Drosophila. Notch ligand Lag2. in nematode There are many kinds of Notch ligands in mammals, and the ligands closely similar to Delta are called Delta single transmembrane proteins[2]. At present, one Notch gene was found in Drosophila and four Notch genes (Notch1, 2,3C4) were found in mammals. Mature Notch acceptor The nucleons are composed of extracellular domains (extracellular Notch,ECN) and transmembrane / intracellular domains (Notch or Delta like Delta-like,Dll), similar to Serrate, called Serrate or Jagged. Human Notch ligands have been found to have Jagged1,Jagged2,Delta1,Delta3,Delta4[4]. The extracellular domain of Notch ligands contains different numbers of EGF like repeats The N-terminal conserved DSL (Delta/ Serrate/ Lag2) domain plays a key role in the binding and activation of Notch receptor[6]. After the ligand of Notch binds to the receptor, the ligand produces receptor-mediated endocytosis. Parks *et al*.[7] showed that the cytosome of the ligand promoted the separation of the receptor heterodimer and the activation of the receptor through the study of Drosophila melanogaster. Compared with Notch receptor, the intracellular domain function of Notch ligand is not very clear. Recent studies have shown that the intracellular domain of Delta1 can induce cell growth inhibition[8].

1.2 Notch signaling pathway

Notch signal transduction pathway is a complex signal sequence composed of a series of molecular events. In the whole signaling pathway, Notch gene encodes Notch receptor proteins. It has gone through three shearing processes. After ribosomal synthesis, the Notch receptor precursor protein encoded by Notch gene was first cut into two fragments by Fringe glycosyltransferase in Golgi body, and then transferred to cell membrane to form a mature Notch receptor. When the Notch ligand binds to the recipient, it triggers the activation of the Notch signal and the activation of the Notch receptor. For the first time, TNF- α -invertase (TNF- α converting enzyme, TACE) hydrolyzed the Notch receptor in the extracellular domain to release the extracellular domain, and the second one was the site cleavage protein (γ -secretase) / early aging protein (presenilin,PS) near the membrane in the transmembrane region. The intracellular domain (intracellular Notch,ICN) was released into the cytoplasm and further transferred to the nucleus[4,10]. γ -secretase is a protein complex composed of PS/NCT/ APH-1/ PEN-2, in which PS contains the active site of γ -secretase[11]. With the participation of cofactors such as MAML in the nucleus, the DNA binding protein CSL (CBF in the nucleus is associated with its RAM domain and cdc/ankyrin complex sequence. 1/Su (H) / Lag- (-1) conjugates and activates HES (hairy/enhancer of split) and other target genes) to activate transcription and play a biological role[4].

2. Notch signal transduction pathway and disease

Notch signal transduction pathway exists widely in vertebrates and non-vertebrates and is highly conserved in evolution. It plays an important role in embryo, cardiovascular, blood cell development and tumorigenesis. Mutations in some molecules or changes in downstream events in the pathway are associated with the occurrence and development of many diseases. A disease related to the Notch signaling pathway that has been identified or lurked prior to introduction.

2.1 Notch signal transduction pathway and tumor

In the process of Notch signal regulating cell differentiation, proliferation and apoptosis, the changes of signal transduction will lead to tumorigenesis. The relationship between Notch signaling pathway and tumorigenesis has been confirmed in T cell leukemia caused by point mutation or chromosome translocation. At present, Notch also occurs in pancreatic adenocarcinoma, neuroblastoma (neuroblastoma) and mucoepidermoid carcinoma (mucoepidermoid carcinoma). Signal change The relationship between Notch signaling pathway and tumorigenesis was first demonstrated in a subtype of human acute T lymphocyte leukemia (T-ALL). This subtype was characterized by the translocation of chromosome t (7; 9) (q34; q34.3), which resulted in the incorporation of Notch1 gene into the T cell receptor β (TCR β) gene and the formation of an active variant of hNotch1, which eventually led to the over-activation of Notch signal[12].

Although t (7) chromosome translocation is only in T-ALL 's In this subtype, however, a further study found that almost all T-ALL overexpressed Notch1 or Notch3[13]. Recent studies have found that mutations in Notch1 activity are present in most T-ALL cases[14]. In addition, Notch receptors and ligands were expressed in various tumor cells and tumor-derived cell lines. Animal experiments further confirmed that overexpression of Notch signal would lead to tumorigenesis. Compared with small cell lung cancer, Notch1,Notch2 *et al*. Notch related molecules are highly expressed in (NSCLC) of many non-small cell lung cancer and have been used in NSCLC cells for colonization and promotion[15]. Notch1 and Notch ligand Delta1, Jagged1 were overexpressed in many kinds of Shenjing colloid fine cytoma[16], Notch3 was highly expressed in renal cell carcinoma[17], and the transcriptional ICN3 expressed in mice could produce T cells. Enhanced expression of Delta4 in Lymphoma[18] The overexpression of Notch1 and Notch3 may induce the occurrence of mammary neoplasms in mice[20]. The development of these tumors may be related to the continuous proliferation of activated Notch receptors by blocking cell differentiation. Studies have shown that carcinogenic events do not necessarily occur at the level of Notch gene expression, but also occur in the lower reaches of the Notch signaling pathway. For example, EB virus can produce an egg white substance called EB nuclear antigen 2 (EBNA2), which Egg white matter can bind to CSL by mimic ICN, thus activating CSL[21]. MAML protein acts as an auxiliary factor in the binding of ICN to CSL, while in mucoepidermoid carcinoma, the MAML gene translocation of t (11; 19) (Q14 / 21; p12 ~ 13) makes MECT1 gene into MAML2 gene. The fusion product[22], which does not depend on CSL and induces Notch target gene epidermis, can induce tumor. In addition, activated N Otch signal can also promote tumor development in a wider range by interacting with other signal pathways. Miyamoto *et al*.[23] found that the activation of Notch signal was an early event in human pancreatic neoplasms, and the expression of Notch receptor and ligand was up-regulated after activation of RAS/MAPK signal. The results of Brumby *et al*[24] also showed that Notch could be used as a co-oncogene of RAS to promote the development of Drosophila epithelioma. In addition, Notch1, etc. Site gene mutants can accelerate the formation and deterioration of lymphoma by synergistic action with Myc[25]. Girard *et al*.[26] were also found. After insertion of precancerous toxin into thymoma of MMTVD/myc transgenic mice, the detection of overexpressed full-length or truncated Notch1, signals suggested that Notch signal might be detected in thymoma of MMTVD/myc transgenic mice. Cooperate with c-Myc to promote tumor formation.

Most of the Notch signals play a carcinogenic role, but in a few cases they inhibit the occurrence and development of tumors, which may be related to the different expression levels of related molecules in the microenvironment or Notch receptor, ligand and other signal pathways of the cell. This difference ultimately affects cell decisions, leading to differences in the fate choices of fine cells in proliferation, cell cycle inhibition, differentiation, self-renewal or apoptosis[27]. Gramantieri *et al*.[28] investigate the Notch receptor (Notch1, 2,3,4) in normal and sclerosing human liver tissues and liver cancer tissues. To evaluate the relationship between Notch signaling pathway and cell transformation and malignancy. Compared with normal liver tissue and sclerosing liver tissue, Notch3, 4 was down-regulated in all 20 liver cancer samples, and Notch1~4,Delta1 and Jagged1 were down-regulated in 13 of them. The authors suggest that this may be related to cell differentiation disorders.

2.2 Notch signal transduction pathway and hereditary diseases

The Notch signaling pathway regulates the development of organisms through evolutionarily conserved intercellular signaling mechanisms. Disrupting the conservative regulatory pathways in the course of development usually leads to congenital genetic diseases. Recent studies have shown that Notch signaling regulates the differentiation and self-renewal of neural stem cells, hematopoietic stem cells, epidermal stem cells, and so on, in oogenesis, embryonic development, myogenesis, neurogenesis, etc. Hematopoiesis and eye development and other processes play an important role. Gene mutations of related molecules in Notch signal transduction pathway have been demonstrated to be associated with CAD ASIL's disease: Alagille syndrome and spinal rib dysplasia. CADASIL disease (cerebral autosomal dominant arteriopathywith subcortical infarcts and leukoencephalopathy), is also called hereditary multiple infarct dementia. It is an autosomal dominant cerebral artery disease with subcortical infarction and white matter encephalopathy. The disease is now thought to be due to the smooth muscle of the blood vessel The mutation of the Notch 3 gene expressed on the cell was caused by the mutation. Most of the cases were related to the deletion or insertion of cysteine

residues in EGF-R (cysteine rich in cysteine) in the extracellular domain of Notch 3. The disulfide bond between the cysteine residue pairs in EGF-R ensures that the Notch receptor is folded correctly, and the loss or insertion of the cysteine residue leads to the conformation change of Notch 3, which leads to its processing. Defects in the transport process affect their interaction with Notch ligands[29].

Alagille syndrome is an autosomal dominant hereditary disease, which can lead to the absence of various tissues and organs, including heart, liver, kidney and so on. It is characterized by normal bile duct deficiency in the liver and bile accumulation in the liver caused by extrahepatic bile duct stenosis. The disease is caused by Jagged1 dose deficiency caused by Jagged 1 gene mutation, which is mainly characterized by missense mutation, deletion, truncation and splicing of protein, which makes it unable to produce normal Jagged 1 translation product[30]. Studies have shown that Jagged 1 can down-regulate vascular function. After Jagged 1 gene silencing, the endothelial cells increased the vascular formation induced by bFGF. The reason for this phenomenon may be that Jagged 1 reduces the responsiveness of endothelial cells by interacting with Notch receptors (mainly Notch 4).[29]

Bulman *et al*.[31] proved by location-cloning study that the mutation of the Delta3 gene can lead to autosomal recessive spinal rib dysplasia (spondylocostal dysostosis, SD), which is mainly characterized by the high conserved internal production of amino acid residues of Delta 3. Missense mutation or production of truncated proteins.

2.3 Other

Alzheimer's disease,AD is the main type of Alzheimer's disease. It is a degenerative disease of the central nervous system with progressive cognitive impairment and memory impairment as its main clinical manifestation. (senile plaque, SP) and neurofibrillar tangles,NFT are the pathological changes. Two of the main features. The main component of the old spot is the β -starch egg. β -amyloid protein, A β is produced by the splicing of amyloid precursor protein (amyloid precursor protein, APP) by β -secretase and γ -secretase / PS. The main components of NFT are fibrous aggregates which are mainly composed of hyperphosphorylated Tau protein. The splicing of APP and Notch receptors is dependent on the γ -secretase / PSN Notch signaling pathway. It may be related to the occurrence and development of AD, and the change of Notch signal has been found in the research related to AD. Berezovska *et al*.[32] the expression of Notch1 in the hippocampus of sporadic AD patients was more than twice as high as that in the control group. Nagarsheth *et al*.[33] showed that the expression of Notch1 in AD was higher than that in the dementia (DLDH) group without characteristic histological changes and the control group by immunohistochemistry. meanwhile Compared with DLDH, the abnormal aggregation of Tau in AD may be related to AD and other neuropathy caused by Tau aggregates.

During mammalian development, the formation of organs such as the heart and renal circulation depends on the specific vascular system that matches it, which affects the veins. The fate of multiple cells in vascular structures such as arteries and capillaries plays a key role in the development and maintenance of the cardiovascular system. The disorder of Notch signaling system, which is an important pathway affecting cell decision, is thought to be associated with some cardiovascular diseases. Animal model studies have shown that it may affect the cardiovascular system in four ways: vascular remodeling, and vascular remodeling. Vascular stability and selective selection of arteriovenous hair (art) Erial-venous specification), heart visceral hair[34]. For example, the mutation of Notch1 gene will affect the reconstruction of blood vessels in the deep matrix of yolk sac, leading to the collapse of the large motor veins in the dorsal part. The mutation of Notch 2 and Jadded 1 gene may cause glomerular capillary plexus defect, right ventricular dysplasia and right translocation of aorta[34]. The cardiovascular system dysplasia in CADASIL's disease and Alagille's syndrome is also caused by Caused by mutations in the Notch 3 or Jagged 1 gene Study on.

3. Notch signal transduction

Pathway as a drug target By deeply studying the relationship between the molecular mechanism of disease and the Notch signal transduction pathway, using the Notch signal transduction pathway as the drug target, it may be possible to achieve the purpose of treating related diseases. In addition, Notch signaling has been proved to be related to the differentiation and proliferation of stem cells such as hematopoietic stem cells and neural stem cells. At present, the study of Notch signal transduction pathway as a drug target mainly focuses on the treatment of tumor and expansion of stem

cells by inhibiting or activating its signal transduction.

3.1 Notch signal transduction pathway inhibition and tumor therapy

Although the Notch signal exhibits tumor inhibition in a few tumors, its signal transduction activation has been proved to be related to the occurrence and development of many kinds of tumors. In the treatment of tumors associated with Notch, the Notch signal transduction pathway can be used as a viable target for selectively killing tumor cells. Inhibition of Notch signal by blocking the proliferation of tumor cells. Notch signal can be achieved by blocking ligand binding. Recombinant fragments containing more than 2 EGF-R can compete with Notch receptor to bind to Notc H ligand to block signal transduction. Rebay *et al*.[5] proved by large-scale deletion mutagenesis that its second EGF repeats 1112 are necessary structures for interaction with Delta in the extracellular domain of Notch acceptor. Notch signal could induce the differentiation of 3T3 L1 cells into adipocytes, and the heavy group polypeptide (rh11) containing the second EGF complex sequence (1112) could significantly inhibit 3T3 L at 10 -7 mol/L. 1 cell differentiation[35]. In addition, monoclonal antibodies,mAbs can also be used as an inhibitor to block the Notch signaling pathway in Notch recipients. It has been proved that rabbit anti rh11-12 mAbs can effectively block the differentiation of 3T3 L1 cells[35]. However, the design of receptor specific blockers is difficult due to the high conserved sequence of several Notch receptors. Design of anti-conservative EGF MAbs, in the -R region may be an effective method to block ligand binding through steric resistance[35].

Inhibiting the activity of Fringe,TACE, γ -secretase and other proteases in order to prevent the maturation of Notch receptor and the production of ICN could inactivate the Notch signal transduction pathway. For example, melanoma cells overexpression of Notch 1 receptor compared with normal proliferative melanocytes, using a small molecule of γ -secretase inhibitor-GSI, can block the processing and activation of Notch1~4. Apoptosis of melanoma cells was induced, while normal melanocytes only inhibited G _ 2 / M phase. Inhibiting the activity of ICN directly is also one of the effective ways to inhibit Notch signaling pathway. This strategy can inhibit the transcriptional activation of downstream genes by inhibiting the formation of CSL-ICN complex or interfering with the binding of other active compounds to CSL-ICN complex. One of the important pathways is that antisense drugs can down-regulate Notch signaling by targeting any part of the signaling pathway.

In recent years, it has been found that some small molecular compounds can inhibit the Notch pathway to achieve the purpose of anti-tumor. Wang *et al*.[37] showed that genistein inhibited the growth of pancreatic cancer cells and induced apoptosis by inhibiting the activity of Notch 1 and nuclear factor kappaB (NF-kappaB) and their interaction.

3.2 Notch signal transduction pathway activation and stem cell amplification

Stem cells are a class of cells with self-renewal (self-renewing) and multi-differentiation potential, which can produce highly differentiated functional fine cells. Notch signaling plays a decisive role in regulating the directional differentiation and self-replication of multipotent stem cells. Stem cell centered regenerative medicine uses normal cells or tissues to replace dysfunctional or damaged cellular tissues, using differentiated cells to treat Alzheimer's disease, Parkinson's disease, and diabetes. Leukaemia and other diseases, Notch signaling pathway by regulating stem cell differentiation and proliferation will be in this Play an important role in a field. In a few cases, such as the differentiation of neural stem cells into astrocytes, Notch signaling pathway promotes differentiation[38]. For many other stem cells, when Notch receptors bind to their ligands, dry fine cells proliferate undifferentiated. When the Notch signal activity is inhibited, the stem cells enter the differentiation process and develop into functional cells. The Notch signal transduction pathway is considered to be one of the most promising research directions to solve the expansion of stem cells. Currently Notch The application of signaling pathway in stem cell regenerative medicine is mainly focused on the expansion and culture of stem cells in vitro through activation of Notch signaling pathway.

Recombinant proteins or peptides from wild Notch ligands are considered effective Notch activators. In vitro experiments have shown that recombinant proteins and peptides derived from Jagged1,Delta1 have Notch activation properties. In the process of stem cell culture, activated Notch signaling pathway can regulate the proliferation and differentiation of stem cells and serve for stem cell biotherapy and tissue engineering. The strategy is to culture stem /

progenitor cells in a medium containing soluble ligands. Or bind the ligands to the solid surface to mimic the ligands in vivo. To culture stem / progenitor cells with a cross-membrane structure. Since each type of cell requires a unique culture condition suitable for it, containing the right amount of cytokines and growth factors, So there are some difficulties in maintaining stem cell culture and tissue engineering by activating Notch pathway, although in the culture of hematopoietic stem cells, Some progress has been made in maintaining stem cell self-renewal by activating the Notch pathway. Human Notch ligand Delta-like 1 (hDll1) was cloned and expressed in[39]. The extracellular domain (hDll-1ext) was detected by colony culture to amplify the original hematopoietic progenitor cells. Han *et al*.[40] constructed the soluble recombinant protein hDll1NDSL (composed of DSL domain and N-terminal sequence) from human hDll1. It can inhibit the differentiation and promote the proliferation of hematopoietic stem cells.

Gene therapy is another effective way to activate Notch signaling.Genetically engineered cells that lack all or most of the extracellular Notch-activated receptors can activate Notch pathways in cell culture and transgenic animals. Activated Notch can inhibit the differentiation of hematopoietic stem/progenitor cells and promote their proliferation. However, because the target gene binds to some viral oncogenic genes, it can be transformed into living cells. There are also potential safety risks in receptor gene therapy.

4. Prospects

During the development of vertebrates and non-vertebrates, the Notch signal expands and solidifies molecular differences between cells, thus playing a key role in determining the fate of cells. Studies have shown that mutations or functional deletions in some of its subunits are related to the occurrence and development of many diseases, such as tumors, hereditary diseases, Alzheimer's disease and so on. Because of the complexity of Notch signal transduction pathway, some molecular mechanisms (such as ligand endocytosis, function of ligand intracellular domain, etc.) are not very clear. The molecular mechanism between Notch signal transduction pathway and disease development (No in tumor) is not clear. There is also a need for further elucidation of the tch signal and the cooperated-use machine system of c-Mycor Ras and so on. However, there are many potential drug targets in the Notch signal transduction pathway, which is based on the further study of the Notch signal transduction pathway and its molecular mechanism with related diseases. Targeting these targets, drugs are designed to block or activate Notch signals, to treat Notch related diseases, or to carry out stem cell tissue engineering in the treatment of Alzheimer's disease and diabetes. Parkinson's disease and other cellular tissue injury or functional regression diseases have important scientific significance and wide application prospects.

References

1. Lu Z Z, Wu Z Z, Liu H J, *et al*. J Exper Hematol, 2003, 11 (3): 222～ 2261Han W, Ye Q, Moore M A. A soluble form of human Delta-like-1 inhibits differentiation of hematopoietic progenitor cells. Blood,2000, 95 (5): 1616～1625
2. Ye Q, Shieh J H, Morrone G, *et al*. Expression of constitutively active Notch4 (Int-3) modulates myeloid proliferation and differentiation and promotes expansion of he mat opoie ticp ro geni tors. Leukemia, 2004, 18 (4): 777～787
3. Bray S. Notch. Curr Biol, 2000, 10 (12): R433～435
4. Steiner H. Uncovering gamma-secretase. Curr Alzheimer Res, 2004, 1 (3): 175～181
5. Zweidler-McKay P A, Pear W S. Notch and T cell malignancy. Semin Cancer Biol, 2004, 14 (5): 329～340
6. Axelson H. Notch signaling and cancer: emerging complexity. Semin Cancer Biol, 2004, 14 (5): 317～319
7. Weng A P, Ferrando A A, Lee W, *et al*. Activating mutations of NOTCH1 in human T cell acute lymphoblastic leukemia. Science, 2004, 306 (5694): 269～271
8. Collins B J, Kleeberger W, Ball D W. Notch in lung development and lung cancer. Semin Cancer Biol, 2004, 14 (5): 357～364
9. Purow B W, Haque R M, Noel M W, *et al*. Expression of Notch-1 and its ligands, Delta-like-1 and Jagged-1, is critical for glioma cell survival and proliferation. Cancer Res, 2005, 65 (6): 2353～2363
10. Rae F K, Stephenson S A, Nicol D L, *et al*. Novel associationof a diverse range of genes with renal cell carcinoma as identified by differential display. Int J Cancer, 2000, 88 (5): 726～732
11. Bellavia D, Campese A F, Alesse E, *et al*. Constitutive activation of NF-kappaB and T-cell leukemia/l ymphoma in Notch3 transgenic mice. EMBO J, 2000, 19 (13): 3337～3348

12. Yan X Q, Sarmiento U, Sun Y, *et al*. A novel Notch ligand, Dll4,induces T-cell leukemia/lymphoma when overexpressed in mice by retroviralmediated gene transfer. Blood, 2001, 98 (13): 3793～3799
13. Hu C, Dievart A, Lupien M, *et al*. Overexpression of activated murine Notch1 and Notch3 in transgenic mice blocks mammary gland development and induces mammary tumors. Am J Pathol,2006, 168 (3): 973～990
14. Zimber-Strobl U, Strobl L J. EBNA2 and Notch signalling in Epstein-Barr virus mediated immortalization of B lymphocytes.Semin Cancer Biol, 2001, 11 (6): 423～434
15. Wu L, Griffin J D. Modulation of Notch signaling by mastermind-like (MAML) transcriptional co-activators and theirinvolvement in tumorigenesis. Semin Cancer Biol, 2004, 14 (5): 348～356
16. Miyamoto Y, Maitra A, Ghosh B. Notch mediates TGF alpha-induced changes in epithelial differentiation during pancreatic tumori genesis. Cancer Cell, 2003, 3 (6): 565～576
17. Brumby A M, Richardson H E. Scribble mutants cooperate with oncogenic Ras or Notch to cause neoplastic overgrowth in Drosophila. EMBO J, 2003, 22 (21): 5769～5779
18. Hoemann C D, Beaulieu N, Girard L, *et al*. Two distinct Notch1 mutant alleles are involved in the induction of T-cell leukemia in c-myc transgenic mice. Mol Cell Biol, 2000, 20 (11): 3831～3842
19.. Girard L, Hanna Z, Beaulieu N. Frequent provirus insertional mutagenesis of Notch1 in thymomas of MMTVD/myc transgenic mice suggests a collaboration of c-myc and Notch1 for oncogenesis.Genes Dev, 1996, 10 (15): 1930～1944
20. Weng A P, Aster J C. Multiple niches for Notch in cancer: context is everything. Curr Opin Genet Dev, 2004, 14 (1): 48～54
21. Gramantieri L, Lacchini M, Giovannini C, *et al*. Expression of the components of the Notch signaling pathway in neoplastic and cirrhotic human liver. J Hepatol, 2004, 40 (Suppl 1): 103
22. Hadchouel M. Notch signalling pathway and human diseases. J Hepatol, 2000, 32 (Suppl 2): l～2
23. Spinner N B, Colliton R P, Crosnier C, *et al*. Jagged1 mutations in alagille syndrome. Hum Mutat, 2001, 17 (1): 18～33
24. Bulman M P, Kusumi K, Frayling T M, *et al*. Mutations in the human delta homologue, DLL3, cause axial skeletal defects in spondylocostal dysostosis. Nat Genet, 2000, 24 (4): 438～441
25. Berezovska O, Xia M Q, Hyman B T. Notch is expressed in adult brain, is coexpressed with presenilin-1, and is altered in Alzheimer disease. J Neuropathol Exp Neurol, 1998, 57 (8): 738～745
26. Nagarsheth M H, Viehman A, Lippa S M, *et al*. Notch-1 immunoexpression is increased in Alzheimer!s and Pick"s disease. J Neurol Sci, 2006, 244 (1～2): 111～116
27. Carrie J, Shawber1, Jessica J, *et al*. Notch: cell fate determination from vascular development to human Vasculopathy. Drug Discov Today: Disease Models, 2004, 1 (3): 351～358
28. Zlobin A, Jang M, Miele L. Toward the rational design of cell fate modifiers: Notch signaling as a target for novel biopharmaceuticals.Curr Pharm Biotechnol, 2000, 1 (1): 83～106
29. Nickoloff B J, Hendrix M J, Pollock P M, *et al*. Notch and NOXA-related pathways in melanoma cells. J Investig DermatolSymp Proc, 2005, 10 (2): 95～104
30. Wang Z, Zhang Y, Banerjee S, *et al*. Inhibition of nuclear factor kappab activity by genistein is mediated via Notch-1 signaling pathway in pancreatic cancer cells. Int J Cancer, 2006, 118 (8): 1930～1936
31. Ge W, Martinowich K, Wu X, *et al*. Notch signaling promotes as trogliogenesis via direct CSL-mediated glial gene activation. J Neurosci Res, 2002, 69 (6): 848～860
32. Lu Shouzhang, Wu Zuze, Liu Hongjun, *et al*. Expression and purification of human Delta-like-1 extracellular domain in CHO cells and its effect on expansion of hematopoietic progenitor cells. Chinese Journal of Experimental Hematology 2003, 11 (3): 222 ~ 22634 Kojika S, Griffin J D. Notch receptors and hematopoiesis. Exp Hematol, 2001, 29 (9): 1041～1052
33. Artavanis-Tsakonas S, Rand M D, Lake R J. Notch signaling: cell fate control and signal integration in development. Science, 1999,284 (5415) : 770～776
34. Rand M D, Grimm L M, Artavanis-Tsakonas S, *et al*. Calcium depletion dissociates and activates heterodimeric notch receptors. Mol Cell Biol, 2000, 20 (5): 1825～1835
35. Nam Y, Aster J C, Blacklow S C. Notch signaling as a therapeutic target. Curr Opin Chem Biol, 2002, 6 (4): 501～509
36. Rebay I, Fleming R J, Fehon R G, *et al*. Specific EGF repeats of Notch mediateinteractions with Delta and Serrate: implications for Notch as amultifunctional receptor. Cell, 1991, 67 (4): 687～699.
37. Milner L A, Bigas A. Notch as a mediator of cell fate determination in hematopoiesis: evidence and speculation. Blood, 1999, 93 (8): 2431～2448.
38. Parks A L, Klueg K M, Stout J R, *et al*. Ligand endocytosis drives receptor dissociation and activation in the Notch pathway. Development, 2000, 127 (7): 1373～1385.
39. Kolev V, Kacer D, Trifonova R, *et al*. The intracellular domain of Notch ligand Delta1 induces cell growth arrest. FEBS Lett, 2005, 579 (25): 5798～5802.

40. Blaumueler C M, Qi H, Zagouras P, *et al*. Intracellular cleavage of Notch leads to a heterodimeric receptor on the plasma membrane. Cell, 1997, 90 (2): 281～291.